REMARKS

Entry of the foregoing, and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 1 and 3 have been amended to further clarify Applicants' invention. Support for the amendments can be found in the Examples of the specification and in the originally filed claims. No new matter has been added nor has the scope of the claims been changed, either literally or for purposes of the doctrine of equivalents.

The Examiner has rejected claims 1, 3 and 7 under 35 U.S.C. § 102(b) as being anticipated by Bewicke (U.S. Patent No. 5,820,867). Applicants respectfully traverse this rejection.

It is well settled law that to anticipate a claim, a single reference must teach each and every element of the claim, and the single reference must be enabling. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Claim 1 is directed to an orally applicable natural formulation comprising St. John's Wort or its extract or active ingredients in combination with one or more derivatives of dihydro- and/or tetrahydrofolic acid or suitable salts thereof.

In contrast, Bewicke discloses a dietary supplement composition that comprises an extract of St. John's Wort, one other anti-depressant herbal extract and four vitamins (see *e.g.*, claim 1 of Bewicke). One of the vitamins may be folic acid (see *e.g.*, claim 4 of Bewicke). Bewicke does not teach the use of dihydro- or tetrahydrofolic acids or salts thereof. Therefore, Bewicke cannot and indeed does not anticipate the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, 3 and 7 under 35 U.S.C. § 102(b).

The Examiner has rejected claims 1-9 under 35 U.S.C. § 103(a) as being unpatentable over Bewicke (U.S. Patent No. 5,820,867). Applicants respectfully traverse this rejection.

As stated above, the present invention relates to an orally applicable natural formulation comprising St. John's Wort or its extract or active ingredients in combination with one or more dihydro- and/or tetrahydrofolic acid compounds or suitable salts thereof.

The Examiner must show that the cited prior art coupled with the general knowledge at the time of the invention contains some suggestion or incentive to motivate a skilled artisan to modify a reference or to combine references to achieve the claimed invention. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). The cited reference Bewicke does not contain such a suggestion or incentive. Bewicke discloses a dietary supplement composition that comprises an extract of St. John's Wort, one other anti-depressant herbal extract and four vitamins. One of the vitamins may be folic acid, although it need not be-see claim 1 of Bewicke. Nowhere does Bewicke mention or suggest the use of dihydro- or tetrahydrofolic acids or salts, much less derivatives thereof such as those of claim 3, in combination with St. John's Wort. With the teachings of Bewicke, the person skilled in the art would therefore have no suggestion (much less any reason) to substitute the folic acid in the compositions of Bewicke with the reduced folates, etc. of the present invention. Thus, the skilled artisan would not be motivated to modify Bewicke to achieve the present invention.

The Examiner must also show that the modification or combination of cited references must have a reasonable expectation of success. This reasonable expectation of success must be provided by the cited references, not Applicants' disclosure. *See In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir.). As stated above, Bewicke does not mention or suggest the use of the reduced folates, etc. of the present invention in combination with St. John's Wort. Thus, not only would the skilled artisan not be motivated to use the teachings of this reference to arrive at the present invention, but also the skilled artisan would not have a reasonable expectation of success in view of the teachings in Bewicke, which does not even discuss metabolism of folic acid to folates (see the specification at p. 4, lines 17-28).

As the Examiner must show that the cited or combined references teach each and every limitation of the claimed invention. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997). Applicants submit that Bewicke does not teach the present composition comprising St. John's Wort or its extract or active ingredients in combination with one or more dihydro- and/or tetrahydrofolic acids or suitable salts thereof.

To further substantiate the inventiveness of the compositions of the present invention over the teachings of Bewicke, two surprising advantages arising from the use of reduced folates instead of folic acid in compositions are described below with reference to the example of 5-methyl-(6S)-tetrahydrofolate.

Further evidence of the non-obviousness of the present invention is present in the later recognition of the advantages of reduced folates, as shown in the attached publications, published

subsequent to the filing and priority dates of the present application. In the first publication, investigations were carried out with 400 µg of folic acid and a corresponding amount of 5-methyl-(6S)-tetrahydrofolate on 23 test subjects. Results (mean value) were presented at a conference in Interlaken, Switzerland (May 29, 2001 to June 1, 2001) and are described in Prinz-Langenohl et al., "Bioavailability of 6S-5-Methyltetrahydrofolate relative to folic acid," Bioavailability May 2001, Interlaken, Switzerland (attached hereto).

The experimental data for each of the 23 test subjects on which the mean values disclosed in the abstract of Prinz-Langenohl et al. were based were presented by Anja-Martina Bohlmann during the Nutritionals 2002 conference in Anaheim, California ("Bioavailability and Other Scientific Aspects About Metafolin," February 5, 2002 to February 7, 2002). A copy of the experimental data is attached hereto.

The test subjects were given a single dose of 400 µg of folic acid and an equimolar amount of 5-methyl-(6S)-tetrahydrofolate. In the study, the total folate concentration (*i.e.*, the concentration of folic acid and 5-methyl-(6S)-tetrahydrofolate together) in the plasma was measured. The first sample collection was carried out just before administration of the above-mentioned substances. Additional plasma samples were collected 1, 2, 3, 4, 6, and 8 hours after the administration. The administration of folic acid and the administration of 5-methyl-(6S)-tetrahydrofolate were separated by a "wash-out period" of 1 week. The methodology of the experiments is described in the abstract of Prinz-Langenohl et al.

Upon administration of 5-methyl-(6S)-tetrahydrofolate, the total folate concentration in all test subjects was at its maximum after 1 hour (see the experimental data for "Metafolin™"). By contrast, it was found that upon administration of folic acid, the highest total folate concentration was not achieved until 2 hours or even longer in a significant portion of the test subjects (see the experimental data for "Folic Acid"). This means that in the case of 5-methyl-(6S)-tetrahydrofolate, the folate is, surprisingly, available earlier.

In addition, upon administration of 5-methyl-(6S)-tetrahydrofolate, the total folate concentration in the blood of the different test subjects is more similar than upon administration of folic acid (compare the experimental data for folic acid and Metafolin™). In the case of Metafolin™, the curves have a significantly higher degree of similarity, which means that the risk of an unfavorable low availability of folate for an individual is significantly reduced. These unexpected results provide further evidence of non-obviousness.

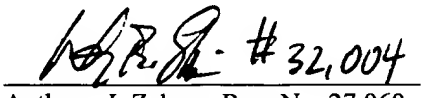
Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-9 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

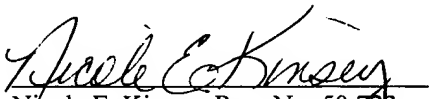
In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney or agent concerning such questions so that prosecution of this application may be expedited.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)



Nicole E. Kinsey, Reg. No. 50,723
Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Date: September 4, 2002

MARKED-UP VERSION OF CLAIMS TO SHOW CHANGES MADE

1. (Amended) ~~Orally~~ An orally applicable natural formulation comprising St. John's Wort (*Hypericum perforatum*) or ~~its extracts~~ an extract or active ~~ingredients~~ ingredient thereof, in combination with at least one ~~derivatives of dihydro- and~~ dihydrofolic acid or salt compound, tetrahydrofolic acid or salt compound or ~~suitable salts~~ a mixture thereof.

3. (Amended) Formulation according to claim 1 comprising a ~~derivative of~~ dihydro- or tetrahydro- folic acid compound selected from the group consisting of 5-methyltetrahydrofolic acid, tetrahydrofolic acid, dihydrofolic acid, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5, 10-methylentetrahydrofolic acid, ~~and~~ 5-methenyltetrahydrofolic acid ~~or their suitable~~ and salts thereof.